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PCT

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Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/036418

International filing date (day/month/year)
01.11.2004

Priority date (day/month/year)
30.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07C235/08, C07C233/18, C07D303/36, C07C271/22, C07C255/26, A61K31/165, A61P25/28

Applicant
ELAN PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 1-18 (all in part), 9-11 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 9-11 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☒ the claims, or said claims Nos. 1-18 (all in part) are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-18 (all in part)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|--|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-13,17,18
	No: Claims	14-16
Inventive step (IS)	Yes: Claims	1-13,17,18
	No: Claims	14-16
Industrial applicability (IA)	Yes: Claims	1-8,12-18
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

10/575824
AP20 Rec'd PCT/PTO 12 APR 2006
International application No.

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1 - 18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to the general formula (I) in which the residue R₁-Y- represents a 3,5-difluorobenzyl group.

Consequently, a complete written opinion concerning the present application is limited to those parts of the claims for which a complete international search report was established (Rule 43bis.1(b) with reference to Rule 66.1(e) PCT).

It should in particular be understood that any positive statement as to novelty and/or inventive step exclusively relates to said limited subject-matter.

Claims 9 - 11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 03/029169 A (ELAN PHARMACEUTICALS), 10 April 2003

D2: WO 03/006013 A (ELAN PHARMACEUTICALS), 23 January 2003

1. Novelty

1.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 14 - 16 is not new in the sense of Article 33(2) PCT.

The document D1 (see D1, page 82, line 8 - page 83, line 23) discloses already the preparation of intermediates disclosed in claims 14 - 16.

1.2 The compounds disclosed in to claim 1 and claim 13 (intermediates) are not disclosed in the available prior art. The subject-matter of claims 1 - 13, 17 and 18 is considered as being novel with respect to the prior art.

2. Inventive Step

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 14 - 16 does not involve an inventive step in the sense of Article 33(3) PCT.

The subject-matter of claims 14 - 16 is not novel. Consequently, it cannot involve an inventive step either.

2.2 The subject-matter of claims 1 - 13, 17 and 18 does meet the criteria of Article 33(3) PCT.

In view of the documents D1 and D2, which can both be regarded as representing the closest prior art, the problem underlying the present application can be defined as providing further compounds with beta-secretase inhibiting activity, which are useful in the treatment of Alzheimer's disease and related diseases. To solve the problem the Applicant provides the compounds of the present application, which differ at least in two structural features from the most relevant prior art compounds described in the documents D1 and D2. The provision of the compounds according to claim 1 of the present application as further beta-secretase inhibitors is thus not obvious with regard to the prior art. Consequently, the provision of the compounds of claim 1, their preparation (claim 12) and the intermediates disclosed in claim 13 involve an inventive step.

3. Industrial Applicability

3.1 The subject-matter of claims 1 - 8 and 12 to 13 is industrial applicable.

3.2 For the assessment of the present claims 9 - 11 on the question whether they are

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industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.